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LETTERS TO THE EDITOR

Blocking of reticuloendothelial cells by dextran

Introduction of an allyl group into the dextran molecule enables a radioactive iodine isotope to be added at the double bond (Brooks, Davies & others 1970; Ricketts, 1966). This labelled dextran is convenient for experiments *in vivo* on the permeability of membranes and has been used in an investigation of the permeability of the renal glomerulus (Hardwicke, Hulme & others, 1968).

In a preliminary experiment with rabbits, an intravenous injection of [^{125}I] dextran was found to disappear from the circulation more slowly when diluted with 6% dextran 110 (B.P. 1963, Addendum, 1966) than with saline. To investigate this phenomenon, random bred rabbits, 3–4 g, of either sex, were given NaI in the drinking water (100 mg/litre) before and during experiments to ensure that the radioactive label was not taken up by the thyroid gland. Injections of [^{125}I]dextran were given through a marginal ear vein and blood samples (about 2 ml) were taken from the opposite ear. Radio-activity was measured on lithium heparin plasma samples. Results are expressed as percentages of the radioactivity in the plasma at zero time; this value being obtained by extrapolation of the values at 10 and 20 min after injection.

To exclude the possibility that the original observation was attributable to biological variation, an experiment of "cross-over" was made in which one rabbit received 12 μCi [^{125}I]dextran (specific activity 0·8mCi/g) in 10 ml of saline and a second rabbit received the same dose of [^{125}I]dextran in 10 ml of 6% dextran 110. Seven days later the experiment was repeated in the same animals with the doses interchanged. Fig. 1A shows that there is little variation between rabbits and that the slower disappearance of radioactivity is associated with the dextran injection.

In a second group of 4 rabbits, given various amounts of 6% dextran 110, the [^{125}I]dextran left the plasma more slowly as the dextran dose increased (Fig. 1B). The [^{125}I]dextran, in all experiments, left the circulation more rapidly than dextran determined chemically after injection of 30 ml of 6% solution, shown by the dotted line in Fig. 1B. The molecular size distribution of the [^{125}I]dextran was known, from gel filtration on columns of Sephadex G-200, to be the same as that of the dextran 110 injected.

At this stage it seemed possible that the observed effect might be due to partial blocking of cells of the reticulo-endothelial system by the dextran. Experiments with mice were therefore designed to test the hypothesis that [^{125}I]dextran is taken up into cells of the reticulo-endothelial system and that this uptake can be influenced by the injection of dextran.

12 mice, 20–30 g, of either sex, were given NaI in the drinking water (50 mg/litre) before and during experiment. Each received an injection of 0·5 ml of saline, containing 0·2 μCi [^{125}I]dextran, through a tail vein, each was anaesthetized with ether, then a cardiac blood sample taken, finally the animals were killed at various times after injection. The urinary bladder was removed and discarded, the liver, spleen, remaining carcase and the blood sample were then separately assayed for radioactivity. The amounts of radioactivity taken up into the cells of the liver and spleen were obtained by subtracting the activity due to the blood in each organ from their measured activities. Standard values for the volumes of blood per gram of liver and spleen were obtained from the Handbook of Circulation (1959) and appropriate corrections made for radioactivity of included blood. The experiment was repeated with injections of 0·18, 1·8 or 6% dextran 110 in place of saline.

The percentage of the injected radioactivity found in the spleen in these experiments was always less than 1%. In four mice selected at random from the saline group, the

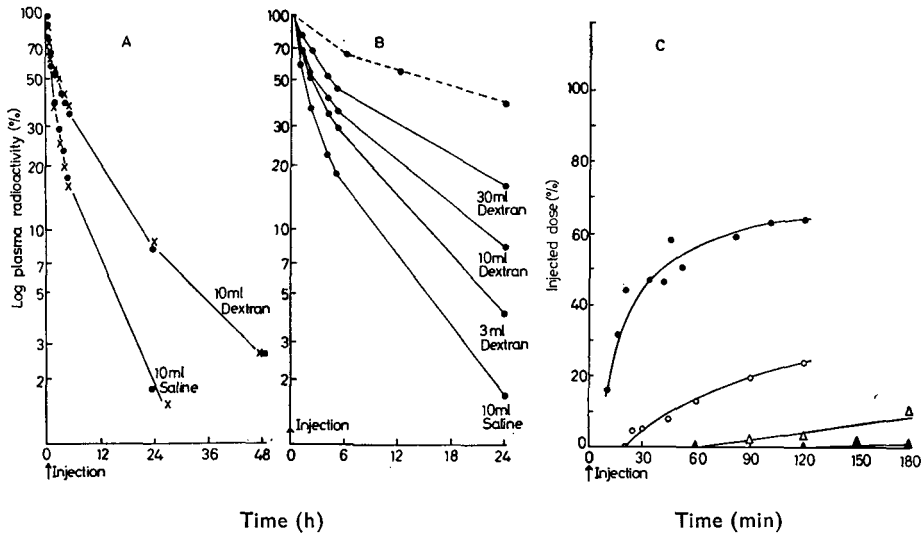

FIG. 1A. Disappearance of radioactivity from the plasma of rabbits given intravenous injections of [^{125}I]dextran. Values are expressed as percentage of the plasma activity at zero time. Rabbit I (×) received (1) [^{125}I]dextran in saline. (2) [^{125}I]dextran in 6% dextran 110 solution. Rabbit II (●) received the same injections in reverse order.

B. Disappearance of radioactivity from the plasma of rabbits given intravenous injections of [^{125}I]dextran diluted with saline or with various volumes of 6% dextran 110. The broken line shows the chemical determination of dextran in plasma after an injection of 30 ml of 6% dextran 110 solutions.

C. Uptake into the liver of [^{125}I]dextran in mice killed at various intervals after intravenous injection. The [^{125}I]dextran was diluted with saline (●), 0·18% dextran (○), 1·8% dextran (△) and 6% dextran (▲).

kidneys and lungs also contained less than 1% of the injected dose. It appears that the liver is mainly responsible for uptake of [^{125}I]dextran. Fig. 1C shows how this uptake is influenced by the inclusion of dextran 110 in the injected dose. When no dextran is present (upper curve), the liver contains some radioactivity 10 min after injection and uptake increases rapidly with time. Comparing this with the other curves in Fig. 1C, it appears that the presence of increasing amounts of dextran in the injected dose delays uptake of [^{125}I]dextran by the liver and reduces the total amount taken up.

These results support the view that dextran partially blocks the reticulo-endothelial cells of the liver responsible for the uptake of [^{125}I]dextran so that more of the labelled material is left in the circulation, as was found in the experiments with rabbits.

The presence of dextran in reticulo-endothelial cells has long been known, but these measurements of the blocking effect by graded doses *in vivo* illustrate the way in which dextran infusions may alter the uptake of bacterial antigens or therapeutic substances by reticulo-endothelial cells.

M.R.C. Industrial Burns Unit,
Birmingham Accident Hospital,
Bath Row,
Birmingham 15, *U.K.*

S. P. FARROW
C. R. RICKETTS

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Screens for anti-inflammatory drugs

It has recently been shown by Willis (1969), Di Rosa, Giroud & Willoughby (1971), Di Rosa, Papadimitriou & Willoughby (1971) that the oedema induced in rats feet by injection of carrageenan is mediated by histamine and 5-hydroxytryptamine (5-HT) during the first hour, after which the increased vascular permeability is maintained by kinin release up to $2\frac{1}{2}$ h. From $2\frac{1}{2}$–6 h the mediator appears to be a prostaglandin, release of which is closely associated with migration of leucocytes into the inflamed site. All the mediators appear to be dependent upon an intact complement system for their activation and release (Giroud & Willoughby, 1970). Examination of the non-steroidal anti-inflammatory drugs on this model has shown that they suppress mainly the last phase of the response, namely the "prostaglandin phase." Their ability to suppress this phase correlates directly with their ability to suppress mononuclear leucocyte migration into the inflamed tissues. Thus the oedema and its suppression during the period $2\frac{1}{2}$–6 h after injection of carrageenan serves as an index of leucocyte migration. It has been suggested that this explains why the model of acute inflammation can successfully be employed in the search for new non-steroidal anti-inflammatory agents (Di Rosa, Papadimitriou & Willoughby, 1971).

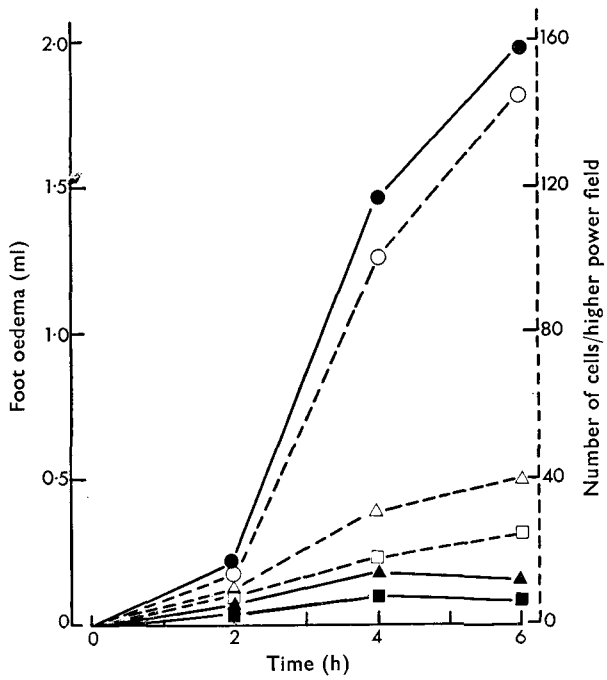

FIG. 1. Foot oedema (solid symbols) and cell emigration (open symbols) in histamine, 5-HT and kininogen-depleted rats after subcutaneous injection (0·1 ml) into the foot of either 1% carrageenan (circles), 6% dextran (triangles) or 1% formalin (squares).